REMARKS/ARGUMENTS

I. Claim Status

Claims 1, 27, 38 and 51 have been amended to recite that the formulation is not a liposomal formulation. The statuses of the claims are as follows:

Claims 3-4, 8-9, and 31 have been canceled.

Claims 6-7, 10-11, 17-20, 22-24, 33, 35-37 and 41-50 have been withdrawn.

Claims 1-2, 5, 12-16, 21, 25-30, 32, 38-40 and 51-69 are pending.

II. Rejections Under 35 USC §103(a)

To establish a prima facie case of obviousness the prior are references must teach or suggest each and every element claimed. The Office has not proven a *prima facie* case of obviousness because none of the references cited teach or suggest the claimed concentration range of a hypertension reducing agent as recited in the claims.

Claims 1-2, 5, 12-16, 21, 25-30, 32, 34, 38-40 and 51-69 have been rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,554,610 to Williams et al. (hereinafter "Williams") in view of U.S. Publication No. 2006/0002992 to Schmehl et al. (hereinafter "Schmehl") or alternatively U.S. Patent No. 5,759,565 to Azaria et al. (hereinafter "Azaria") or alternatively in view of U.S. Publication No. 2001/0031738 to Schwarz (hereinafter "Schwarz").

A. The Cited References do not Teach or Suggest the Claimed Concentration Ranges

Williams is generally directed to methods of treating disorders associated with pulmonary hypertension by administering a given dose (mg) of a vasodilator either from one to four times per day. Specifically, Williams provides the following:

> [A] unit dose will normally contain 0.01 to 50 mg for example 0.01 to 10 mg, of the Compound, or a pharmaceutically acceptable salt thereof. Unit doses will normally be administered once or more than once a day, for example 2, 3, or 4 times a day, more usually 1 to 3 times a day such that the total daily dose is normally in the range of 0.0001 to 1 mg/kg...

See Williams at column 2, line 20 continuing through line 29.

However, Williams does not explicitly teach or suggest a concentration range of 0.1 to 15 mg/ml as recited in Claims 1, 27, 38, and 51. Williams, at no point, discusses or references any

vasodilator concentration (mg/ml). Williams is silent regarding any suitable or potential fill volume that could be used in conjunction with the disclosed dosages to provide or suggest a suitable vasodilator concentration. Additionally, Williams does not discuss how a particular dosage or particular vasodilator may impact the selection of a suitable fill volume. For instance, Williams broadly defines a vasodilator to encompass numerous different compounds each with different properties (e.g. solubility), but neglects to provide any teaching as to how different doses of these different compounds will most likely require different fill volumes and/or excipients to formulate an inhalable composition capable of being adequately administered to the respiratory tract.

Further, the broad range of dosages and active compounds will necessarily impact the properties of the final inhalable composition, namely the viscosity and surface tension. Since viscosity and surface tension have a direct impact on the aerosolized particle size distribution (key to targeting the appropriate location for depositing the active agent), it is likely that specific dosages within Williams broad dosage range exhibit significantly different efficacies, if any at all, when formulated with the same or similar fill volumes. Additional excipients or co-solvents could possibly be used to mitigate an undesirable viscosity or surface tension, but continued addition will ultimately impact the fill volume for such formulations. Williams does not provide any teaching that would allow one skilled in the art to delineate which dosages would require additional components and/or larger or smaller fill volumes. Accordingly, Williams does not provide any guidance as to any particular dosage nor any particular concentration for such a dosage. Therefore, Williams simply does not explicitly teach or suggest any vasodilator concentration, much less the currently claimed range.

Since the claimed concentration ranges are obviously not explicitly taught or suggested by Williams, it appears that the Office is asserting that Williams inherently teaches or suggests the currently claimed concentration ranges. Thus, the Office must provide the rationale or evidence to support a showing of inherency. See MPEP 2112 (IV). Williams does not inherently disclose the claimed concentration ranges.

"To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would

be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). However, the Office has not provided any rationale or evidence to support such an assertion.

For Williams to inherently disclose the currently claimed concentration ranges, the claimed concentration ranges must necessarily be present from the dosage teachings of Williams. Furthermore, the possibility that one might potentially be capable of selecting a specific dosage from Williams and a fill volume such that a concentration is back-calculated to fall within the currently claimed range is not enough to establish inherency. The prior art must provide some teaching that would provide the Office a factual or technical basis for such an assertion. Given the broad unit dosage ranges mentioned by Williams, namely 0.01 to 50 mg, and the complete lack of guidance as to an appropriate dosage within this broad range in conjunction with a suitable fill volume, as discussed in detail above, there is no basis for selecting one specific dosage over another. Applicant notes that Williams, regarding a unit dose, merely states "...for example 0.01 to 10 mg..." Williams provides no further support for this example or why one might be inclined to use a dosage within the 0.01 to 10 mg range as opposed to a dosage outside this range. Additionally, this range is also quite large and Williams has similarly not provided any teaching that would incite one skilled in the art to select a particular dosage within this range. Specifically, one skilled in the art would have no basis, from Williams, for selecting a dosage of, for example, 0.05 mg instead of 9 mg. Likewise, the Office has no factual or technical basis for selecting a particular dosage from Williams and applying this to a non-disclosed fill volume to establish inherency of the claimed concentration ranges. Therefore, Williams does not inherently teach or suggest the currently claimed concentration ranges.

Accordingly, Williams does not explicitly of inherently teach or suggest each an every element, namely the currently claimed concentration ranges, of independent claims 1, 27, 38 and

51. Applicant notes that the Office has not provided the Applicant with the necessary explanation as to why "the missing descriptive matter" (i.e. concentrations) is necessarily present in the teachings of Williams. Applicants request the withdrawal of this rejection or at least the courtesy of removing the finality of this action and providing Applicant with the factual and/or technical basis upon which this rejection was made so that Applicant may have a fair opportunity to address the Office's basis for the rejection.

In general, Schmehl is directed to liposomal formulations for pulmonary application, wherein the liposomes release encapsulated drug compounds in a controlled manner. Schmehl teaches that the frequency of administration of vasodilators for the treatment of pulmonary hypertension may be reduced by providing a sustained-release liposomal formulation. The liposome components, DPPC and cholesterol are present at a molar ratio of 7:3 and 7:4, respectively. Schmehl also provides the release kinetics from liposomes for carboxyfluorescein. However, Schmehl does not provide any discussion regarding concentration ranges of hypertension reducing agents, much less the claimed concentration range for a non-liposomal formulation. Accordingly, Schmehl does not teach of suggest the currently claimed concentration ranges recited or non-liposomal formulations as recited in independent claims 1, 27, 38 and 51.

Azaria is directed to galenic compositions for nasal administration including a calcitonin as the active agent. Calcitonins are long chain polypeptides used in the treatment of Paget's disease, hypercalcaemia and osteoporsis. The compositions described by Azaria are adapted for administration in the form of a nasal spray. However, Azaria is silent regarding hypertension reducing agents and concentration ranges of hypertension reducing agents for inhalable formulations. Accordingly, Azaria also does not teach or suggest the currently claimed concentration ranges.

Schwarz is directed to formulations for inhibiting endothelial-monocyte activating polypeptide II (EMAP II). More specifically, Schwarz is directed to a method of administering a formulation utilizing an active compound that "inhibits EMAP II activity, including compounds that specifically bind to EMAP II (e.g., an antibody), compounds that downregulate EMAP II expression (e.g., an antisense oligonucleotide), or EMAP II receptor antagonists." Schwarz

generically discloses administering such an active compound either alone or in conjunction with another compound known to be useful in treating pulmonary hypertension such as a calcium-channel blocker, angiotensin-converting enzyme inhibitors, nitrous oxide, L-arginine, and digoxin. Therefore, the formulations according to Schwarz must include a compound that inhibits EMAP II activity (e.g., an antibody, an antisense oligonucleotide, or a receptor antagonist). Schwarz provides some dosage teachings based on the active compound, wherein the active compound is one that inhibits EMAP II activity (e.g., an antibody, an antisense oligonucleotide, or a receptor antagonist). See page 3, paragraph 27. Therefore, Schwarz also fails to teach the concentration ranges for the hypertension reducing agents recited in independent claims 1, 27, 38 and 51.

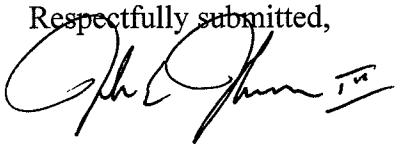
Since the cited references all fail to teach or suggest the currently claimed concentration range of a hypertension reducing agent as recited in independent claims 1, 27, 38 and 51, any combination of Williams and Schmehl, Azaria or Schwarz also fails to teach or suggest the currently claimed range of a hypertension reducing agent. Applicant submits that the obviousness rejection has been overcome and requests withdrawal of this rejection.

III. Conclusion

In view of the amendments and remarks made above, Applicant submits that the pending claims are now in condition for allowance. Applicant respectfully requests that the claims be allowed to issue. If the Examiner wishes to discuss the application or the comments herein, the Examiner is urged to contact the undersigned by telephone.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,



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